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Auricchio, Angelo

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Pacing-Correctable Mitral Regurgitation Something Old, Something New

Angelo Auricchio, MD, PhD, FESC

Mitral valve regurgitation (MR) is a rather common finding in heart failure (HF) patients with ischemic or nonischemic cardiomyopathy.^{1,2} MR is a progressive disease as it causes chronic left ventricular (LV) volume overload, increases right ventricular (RV) pressure, and thereby accelerates the progression of LV dysfunction and HF. There is ample evidence about the close relationship existing between MR, hospitalization rate, and overall survival.^{3,4} About 25% to 65% of HF patients present MR of variable severity.^{1,5} In the presence of ventricular conduction abnormalities, the proportion of HF patients with MR substantially increases. Up to 80% to 85% of patients undergoing cardiac resynchronization therapy (CRT) present MR, being of moderate to severe degree in $\approx 40\%$ of cases.⁶⁻⁸ Thus, patients with ventricular conduction abnormality are at increased risk of worsening HF, hospitalization, and death.⁹ The pathophysiological cascade responsible for higher prevalence of MR in CRT patients has been extensively discussed in a recent review by Spartera et al.¹⁰ In addition to well-known anatomic alterations causing MR in patients with HF, the presence of spontaneous or pacing-induced ventricular conduction abnormalities (1) further decreases closing forces acting on the mitral leaflets because of less efficient myocardial fiber contraction, (2) accentuates tethering forces because of abnormal timing of papillary muscles contraction together with the lack of leaflet coaptation, (3) contributes to additional systodiastolic distortion of the mitral valve apparatus and its abnormal deformation; and finally (4) provokes diastolic MR because of the appearance of a diastolic ventriculoatrial gradient as a result of abnormal atrioventricular timing. In those HF patients with ischemic cardiomyopathy and ventricular conduction abnormalities, the presence of scar tissue in proximity or involving a papillary muscle adds a structural component to the MR.

See Article by Chatterjee et al

The development of a treatment strategy to reduce MR in patients with represents an intense research area including catheter-based interventions, surgical minimally invasive

approaches, and the use of CRT.¹¹⁻¹⁴ Significant decrease in MR after CRT has been observed in a substantial proportion of patients and attributed to a complex interaction of mechanisms, including recoordination of the papillary muscle closing forces, reduction in LV volumes with a decrease in mitral leaflet tenting angles, and augmentation of transmitral pressure gradient by cause of increased contractility.¹⁰ Because of amelioration or complete correction of MR by CRT, reduced LV filling pressures, decreased postcapillary pulmonary congestion, and reverse cardiac remodeling have been observed.¹⁰ Moreover, relief of HF symptoms, decrease in hospitalization rates, and reduction in cardiovascular mortality have been consistently reported by several studies conducted in CRT patients presenting with MR.¹⁰

When treating HF patients with CRT, the big dilemma is whether the patient will benefit by this costly therapy (although CRT is one of the most cost-effective therapies in HF). Over the past 2 decades, numerous invasive and noninvasive predictors of the response to CRT have been proposed. Among the others, a common studied measure of electric delay is the QLV interval, ie, the time from the onset of the QRS complex on the surface ECG to the local LV activation at the site of the LV lead.^{15,16} Lead positioning guided by physiological parameters (late electric or mechanical activation) rather than by anatomic location has shown a greater predictive value for a variety of outcome measures.^{15,17-19} Previous studies demonstrated the predictive value of QLV interval as a measure of LV electric delay for acute hemodynamic changes and clinical outcome with CRT. More recently, Gold et al¹⁹ reported in a prospectively designed substudy of the SMART-AV trial (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in CRT) a robust association of the RV-LV interval duration with chronic CRT response, including ventricular remodeling end points and quality of life. RV lead activation time represents a good surrogate of the initiation of ventricular activation, particularly when left bundle branch block (LBBB) is present. The graded response with increasing RV-LV interval duration gives further support to the value of this measure. Interestingly, this relationship was observed in all major subgroups, indicating that a longer RV-LV delay duration predicts a better response than parameters associated with traditionally lower CRT response rates, such as non-LBBB or QRS duration <150 ms. Gold et al¹⁹ speculated that the higher nonresponder rates observed in the presence of non-LBBB and QRS duration of <150 ms was because of a decreased probability of sufficiently long electric delay at anatomically guided lead positions. In support of this hypothesis, patients with non-LBBB and long RV-LV interval duration had more than a 2-fold change in left ventricular end-systolic volume compared with LBBB patients

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From the Division of Cardiology, Fondazione Cardiocentro Ticino, and Centre for Computational Modeling in Cardiology, Università della Svizzera Italiana, Lugano, Switzerland.

Correspondence to Angelo Auricchio, MD, PhD, Division of Cardiology, Fondazione Cardiocentro Ticino, Via Tesserete 48, CH-6900 Lugano, Switzerland. E-mail angelo.auricchio@cardiocentro.org

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with short RV–LV delay duration. Under certain conditions, RV–LV delay duration and QLV may be interpreted as equivalent measures of LV electric ventricular delay (albeit not in the absolute value) and together demonstrate the ability of simple electric measurements to predict improvement in a variety of soft end points after CRT.

The physiopathological link between a simple electric measurement such as QLV and improvement in MR has been recently provided by Upadhyay et al.⁸ These authors confirmed past findings that lower degree of baseline MR and greater improvement in MR at 6 months were associated with reduced HF hospitalization and mortality after CRT. However, this study significantly extended previous knowledge demonstrating that greater changes in MR were achieved by targeting the LV lead in regions of longer QLV at implant.

In this issue, Chatterjee et al²⁰ have analyzed data from patients enrolled in the SMART-AV study and provided strong evidence of the association between baseline QLV and reduction in MR after CRT. These authors should be congratulated because, by using an extremely robust methodological and statistical approach, they contributed to a mechanistic basis for the adoption of an electric-targeting LV lead strategy at the time of CRT implant. Chatterjee et al²⁰ selected 426 patients representing ≈50% of the original SMART-AV study where serial echocardiography and interpretable baseline QLV measurements were available. Moreover, final LV lead position and echocardiography-based measurements of intraventricular dyssynchrony, quantified as the time from QRS onset to peak systolic velocity adjacent to the annulus at the LV base in 6 myocardial segments, were included in the analysis. Moreover, dyssynchrony—measured at LV segments adjacent to papillary muscles—was additionally assessed. In unadjusted analysis stratified by median QLV (95 ms), longer QLV was associated with less severe MR at 6 months, and larger reductions of left atrial volume and filling pressure. Notably in the MADIT-CRT study (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), CRT patients with LBBB and complete left-sided reverse remodeling had significantly lower risks of HF and death, solely HF, and solely death during long-term follow-up than patients with discordant or lesser reverse remodeling.²¹ Even after multivariable adjustment, QLV remained a significant predictor of decrease in MR at 6 months. Interestingly, there was a linear relationship between QLV and MR response.

The study by Chatterjee et al²⁰ contains many additional clinical important observations.²⁰ The potential mechanism of QLV-mediated MR reduction at 6 months was explored by evaluating LV resynchronization and LV reverse remodeling. A longer QLV (\geq versus $<$ median) was associated with greater reduction in LV dyssynchrony and greater LV reverse remodeling. In contrast and very surprisingly, 3-month changes in mechanical dyssynchrony were not associated with the 6-month MR reduction and furthermore did not attenuate the relationship between QLV and 6-month MR reduction. These data, together with the recent results by Upadhyay et al,⁸ suggest that MR improvement mechanistically appeared to be mediated by a reduction in tethering forces achieved through favorable LV reverse remodeling, thus contributing to better understanding the relationship between QLV and MR

reduction. Therefore, rather than conducting extensive pre-implantation assessment searching for the area with the most delayed mechanical segment to be targeted at the time of lead implantation, selecting an area with long QLV at the time of implantation is sufficient to achieve significant MR reduction and reverse remodeling.

The lack of correlation between anatomic lead location and QLV confirms that the solely anatomy-driven LV lead implantation strategy is suboptimal and it calls for more extensive use of multipolar LV lead with possibly independent pacing cathodes.^{22,23} Indeed, in a recent study by van Stipdonk et al,²² delayed LV lateral wall activation (defined as the area where the maximal activation time measured at the LV lateral wall was $>75\%$ of the total QRS duration) was found in approximately half of the patients. In these patients, the location of the latest activated region was more frequently confined to the basal lateral wall, but some individual differences have been observed. In contrast, patients without delayed activation showed more heterogeneous distribution of the latest activated region on the LV lateral wall. The systematic evaluation of LV electric delay by QLV or RV–LV interval duration at the time of LV lead implantation seems reasonable. It suggests repositioning or using different electrodes (ideally a multipolar electrode) with longer electric delays for pacing when short intervals are observed. This finding has an increased importance in subgroups with lower response rates, such as non-LBBB or ischemic cardiomyopathy as recently indicated by Gold et al.¹⁹ These are groups where the LV activation sequence would likely be less predictable because of abnormal LV ventricular activation or scar patterns. It is important to note that, although measurements of LV electric ventricular delay, such as QLV or RV–LV, are of great help in identifying regions where pacing results in an improved outcome, epicardial mapping via the coronary veins is still limited by coronary venous anatomy, and some areas cannot be mapped because they do not contain any vein. As a result, the ultimate proof that pacing at LV electric ventricular delay (whenever endocardially or epicardially located) should be achieved by any means is still missing.

Although American Heart Association/American College of Cardiology guidelines on valvular heart disease recommend the use of CRT for patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy (Level of Evidence A),²⁴ current ESC guidelines on valvular heart disease vaguely refer to the use of CRT in HF patients and MR.²⁵ However, considering the large body of evidence including the present work by Chatterjee et al,²⁰ it is reasonable to claim for early adoption of CRT in MR patients with abnormal QRS duration and HF. Moreover, as indicated by Chatterjee et al,²⁰ the possibility to predict MR improvement by QLV criteria opens the theoretical possibility to correct MR by pacing at much earlier stage of disease rather than considering other established or in-development percutaneous interventions. Invasive coronary venous electroanatomic mapping eventually integrated with delayed enhancement cardiac magnetic resonance could easily be included in the workup of patients with MR and HF.²⁶ This subject needs to be addressed in a future proof-of-concept study followed by prospective randomized controlled trials.

Does the study by Chatterjee et al²⁰ provide all the answers to our questions? Probably not! Long-term results are still warranted in a larger cohort and possibly evaluating hard end points. Importantly, it is not clear whether there is a dynamic change of QLV that may be reflective of reverse structural or electric remodeling, thus necessitating continuous assessment of QLV and readjustment of pacing strategy. Moreover, this study does not provide sufficient information about the outcome of patients with long QLV, in which the MR increased or remained unchanged after CRT. By study design, patients with persistent or permanent atrial fibrillation were not included. It is unclear whether in the presence of additional important comorbidities, such as severe renal failure, a long QLV would be equally predictive of MR reduction, improved quality of life, reversal of LV remodeling, reduction of unplanned HF hospitalization, and mortality. Finally, the role of scar in modulating the outcome has not been elucidated; it is possible that in some patients scar areas correspond to those presenting long QLV, thus being less suitable for pacing. Despite these and other limitations already outlined by the authors, the study by Chatterjee et al¹⁹ deserves recognition.

In conclusion, the measurement of LV electric ventricular delay, such as QLV or RV–LV, is simple, does not require echocardiography or surface electrocardiographic measurements, and has the potential to be measured automatically by devices that would further simplify lead optimization. The possibility that the long QLV could be a marker and possibly a target of pacing-correctable MR would open novel treatment scenarios to be researched.

Disclosures

Dr Auricchio is a consultant for Boston Scientific, Medtronic, LivaNova and receives speaker fees from Medtronic, Boston Scientific, and LivaNova.

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